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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,641	10/07/2005	Russell Gene Higuchi	21634-US2	1928

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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08/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,641	HIGUCHI ET AL.	
	Examiner	Art Unit	
	Sarae Bausch PhD	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/1/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,11-21,23-25,32-40 and 52-78* is/are pending in the application.

4a) Of the above claim(s) *52-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,11-21,23-25 and 32-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-2, 5, 11-21, 23-25, 32-40 and 52-78 are pending in the instant application. Claims 52-78 have been withdrawn from consideration as being drawn to a nonelected invention. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Response to arguments follow. This action is FINAL.

Claim Status

2. The amendment to the claims filed on 06/01/2009 does not comply with the requirement of 37 CFR 1.121 because claims 52-78 are indicated as previously withdrawn and do not contain the text of the withdrawn claims. However, the nature of the non-compliance does not preclude examination of the invention as the non-compliance is directed to withdrawn claims. Therefore, since the reply appears to be bona fide and in the interest of compact prosecution the claims have been examined. However, for any response to this office action to be fully responsive, applicant is required to include the proper markings to indicate the changes that have been made as well as the proper status identifiers for the claims to comply with 37 CFR 1.121.

Claim Rejections - 35 USC § 112-Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 5, 11-21, 23-25, 32-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in the office action mailed 03/21/2008 and has been rewritten to address the amendment to the claims.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for a determining obesity or osteoporosis comprising detecting presence of the A allele of G19524A in the FRZB gene wherein the A allele of G19524A provides indication of osteoporosis or obesity-related polymorphism in a frizzled related protein gene in a nucleic acid sample from an individual. The rejected claims provide no structural limitation regarding A allele of G19524A in the FRZB gene an osteoporosis or obesity related polymorphism in a frizzled related protein gene.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of any frizzled related protein gene (encompasses Frzb1-4, secreted frizzled related genes,etc) with an A at any position that corresponds to 19524 within any frizzled related gene in any organism. Thus the claims encompass the detection of any of the many different nucleic acids wherein the nucleic acid

sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The specification of the instant application discloses one nucleic acid sequence, SEQ ID No. 1 by their complete structure. The specification lists polymorphisms of SEQ ID No. 1, see table 1, however the specification only discloses 11 polymorphisms within SEQ ID No. 1 of which only one is associated with BMI (see table 4) and one is associated with vertebral fracture (see table 5), and therefore the specification does not provide a representative number of polymorphisms of position 19524 in a frizzled related protein gene in an individual that are associated with obesity or osteoporosis. Furthermore, the specification does not disclose the nucleic acid or amino acid structure for other frizzled-related proteins or secreted frizzled related proteins. For example, the specification teaches SEQ ID No. 1 however the specification does not disclose the genomic sequence of other frizzled-related proteins or secreted frizzled related proteins. In addition, there are currently eight known species of FRZB (see gene card, page 7). The specification does not provide any disclosure as to the association of a the A allele of G19524A in each of these genes to diagnosis of obesity or osteoporosis.

The instant specification provides the sequence of SEQ ID No. 1 which corresponds to the frizzled-related protein 1, secreted frizzled-related protein 3 and 11 polymorphic variations of SEQ ID no. 1, of which only 2 variants show an association with either obesity or osteoporosis (see table 4 and 5). Furthermore, the frizzled-related protein 1 has 128 known polymorphisms (see genecard, pg. 9) and the specification does not provide a representative number of position

19524 within the frizzled-related protein 1 in any species that are associated with obesity or osteoporosis.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the polymorphic sequences of SEQ ID no. 1. The specification does not provide any characteristics that would allow one to identify any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of obesity or osteoporosis based on detection of the non-disclosed gene of position 19524.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of the frizzled related gene and association with obesity or osteoporosis, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention

and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for detecting the presence of a frizzled related protein gene polymorphism at position 19524 and its associated with either obesity or osteoporosis in an individual.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

5. The response traverses the rejection on pages 8-12 of the comments mailed 06/01/2009. The response asserts that the amendment to the claims are moot and the specification only examines FRZB gene in humans and thus the homologs and expression variants of FRZB among different species and only one single genomic sequence is references in the claims. The response further asserts that the claims are not drawn to predicting obesity or osteoporosis but determining risk. These remarks have been thoroughly reviewed but not found persuasive. The claims are not limited to detecting position 19524 of SEQ ID NO 1 nor are the claims limited to humans. Although the claims are read in light of the specification, the limitations from the specification are not read into the claims. The specification does not explicitly define the FRZB gene nor define individual. The specification does describe individual as encompassing any mammal, including human and belong to any race or population (See pg. 23, lines 21-22), therefore the

claims include any mammal. Thus the claims are given their broadest reasonable interpretation to encompass individual to include human and non-humans and FRZB gene to encompass homologs and expression variants of FRZB. Therefore, the claims are not described as the specification does not include a representative number of species, human and non-humans with an A allele at position 19524 that is indicative of osteoporosis or obesity nor does the specification describe position 19524 in a representative number of FRZB genes. Additionally, the examiner does acknowledge that the claims are drawn to determining risk for osteoporosis and obesity however the claims still require the knowledge that the polymorphism is associated with obesity and osteoporerosis. Thus the amendment to the claims does not overcome the rejection of record because the claims encompass any human or non-human individual and any FRZB gene.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112- Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 5, 11-21, 23-25, 32-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was previously presented in office action mailed 03/21/2008 and is reiterated below.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the determining an individual's risk for obesity or osteoporosis comprising detecting presence of the A allele of G19524A in a frizzled related protein gene (FRZB) in a nucleic acid sample in an individual. The claims encompass determining an increased or decreased risk of obesity or osteoporosis. Additional claims include polymorphisms that are predisposing or protective in FRZB. The claims are further drawn to presence of a polymorphism inherited from an individual's parent.

The rejected claims encompass analysis of any individual, including human and non-human. The rejected claims encompass any type of osteoporosis. The rejected claims encompass any frizzled related protein gene, including secreted frizzled related protein genes.

The nature of the claims requires knowledge of a correlation between detection of the presence of the A allele of G19524A in FRZB and predisposition to develop osteoporosis or risk for obesity.

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification teaches the present invention is related to methods for detecting an individuals risk for obesity and/or osteoporosis by identifying the presence of at least one polymorphism in the FRZB gene (See pg. 1, lines 5-10). The specification teaches an individuals risk for obesity can be either an increase or decreased risk as compared to an individual without the at least one polymorphism (see pg. 3, lines 5-10). The specification teaches that the at least one polymorphism can be any suitable polymorphism (see pg. 3, lines 10-11). The specification teaches that the nucleic acid sample can be detected by any of the variety of methods known in the art (see pg. 3, lines 29-31). The specification teaches that the individual can be any mammal, including human and belong to any race or population (See pg. 23, lines 21-22). Although detection of nucleic acids and detection of polymorphisms is routine in the art, predictably correlating any polymorphism in the FRZB gene with risk for osteoporosis and/or obesity in any human or non-human individual is unpredictable and the specification does not predictably correlate a representative number of polymorphism of the A allele of G19524A in the FRZB gene with obesity or osteoporosis in any human or non-human individual.

The specification teaches the invention provides for detecting an individual's increased or decreased risk for obesity or osteoporosis by detecting the presence of one or more FRZB SNPs wherein the presence indicated individuals increased or decreased risk for obesity or osteoporosis (see pg 27, lines 9-20). The specification does not provide any guidance on how the presence of one FRZB SNP can determine both an increased and decreased risk of obesity or osteoporosis. Furthermore, the specification does not provide any guidance on how one polymorphism can be both protective as well as predisposing to obesity and osteoporosis. Additionally, the specification does not provide any guidance on polymorphisms inherited from an individual parents and their association with obesity or osteoporosis.

The specification demonstrates a working example of pooling DNA samples from patients with either hip fracture (275 patients), vertebral fracture (262 patients), low bone mineral density (276 patients), control (278 patients), along with patients with a high BMI (141 samples) and low BIM (82 samples) (see pg. 49, lines 10-16). The specification asserts that a significant association between an increased BMI and FRZB_G19524A SNP was demonstrated ($p<.05$) and the A allele of G19524 was associated with increased BMI (see pg. 50, lines 13-18). The specification asserts that a lesser association between increased incidence of hip fracture and FRZB_G19524A SNP ($p<.01$) and asserts that the G allele of G19524A was demonstrated to be associated with increases incidence of hip fracture (see pg. 50 lines 23-30). However, the specification provides is no data for the association of G19524A allele and its association with increase, decrease, protective, or predisposition for osteoporosis.

Table 4 presents the data for the association of the G195424A allele and high and low BMI in women. Table 4 presents two p values, overall distribution of G19524A of $p=.0051$ and

model where 19524A is recessive allele, p=.0032, however it is unclear if the p values represent the association of the homozygous or heterozygous G allele or A allele of 19524.

The data presented in examples 1-2 does not demonstrate a representative number of polymorphisms within the FRZB gene that are predictably associated with osteoporosis or obesity and therefore does not provide any guidance on how to predictably correlate A allele of G19524A in the FRZB gene with increased, decreased, protective, and predisposition to obesity or osteoporosis as the specification does not teach either the G or the A allele as being predictably associated with increased, decreased, protective and predisposing to obesity or osteoporosis.

The specification does not teach any analysis of any non-human individuals. The specification teaches that FRZB gene is a small component of the complex system of genes associated with obesity and osteoporosis and the effect of the FRZB locus is expected to be variable. The specification teaches that other factors such as eating habits, exercise, diet, general health, and the presence of associated diseases may exert dominating effects which in some cases may mask the effect of the FRZB genotype. The specification further teaches that the allele frequencies at other loci relevant to weight and bone related diseases differ between populations and thus populations exhibit different risks for such diseases and therefore it is expected to that the effect of the FRZB genotype may be different in some populations (See pg. 53, lines 1-15). Therefore it can be concluded from the specification that it is unpredictable to correlate any one polymorphism in the FRZB gene in any individual with obesity or osteoporosis, as both disorders involve a complex system of genes, other associated diseases and environmental

factors may dominate the effects of the genotype, and the effect of the FRZB genotype may be different in different populations.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphisms of the FRZB gene are predictably correlative to increased and decreased risk of obesity or osteoporosis. The specification provides no guidance on how the same allele can be both an indicator for increased and decreased risk as well as both protective and diagnostic for obesity and osteoporosis. The specification does not provide reasonable guidance which allele, G or A, at 19524 homozygous or heterozygous is statistically associated with high BMI in females. The specification does not provide any analysis of any polymorphism within the FRZB gene and its association with increased BMI within a male population. The specification provides no statistically significant data to provide guidance on the association of the G or A allele of 19524 with osteoporosis. Although the specification shows a potential relationship of high BMI in women with the presence of the A allele at position 19524, the specification does not clearly provide guidance that demonstrates the presence of A allele, either homozygous or heterozygous at position 19524 is predictably associated with increased risk of high BMI in women.

The unpredictability of the art, level of skill in the art, and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in FRZB gene and predisposition in any individual for obesity or osteoporosis, or determination of 19524 allele in obesity or osteoporosis.

It is unpredictable as to whether or not a sequence comprising FRZB and the position of 19524 as a SNP exists in any non-human organisms, and whether or not detection of a polymorphism in such a sequence in any other organism would be predictive of the risk of obesity or osteoporosis. For example, Mummidi et al. (2000). Mummidi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1st full paragraph). Thus it is entirely unpredictable as to whether or not any polymorphism, including the specifically claimed polymorphic positions would be associated with obesity or osteoporosis.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed

that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong.

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands)

might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Additionally, post filing art Ikegawa et al. (Curr Opin Rheumatol 2007 19(5):429-434) teaches that the association of two polymorphisms within the FRZB is not associated with osteoporosis in all population s (See pg. 2, FRZB). Ikegawa teaches that two variants increase the risk of knee and hip osteoarthritic in Caucasian women but not in men. Ikegawa et al. teaches that in a Spanish population no direct replication of the association of the same two polymorphisms was obtained (see pg. 2 last para). Therefore there is evidence in the post filing art that polymorphisms within the FRZB gene in different populations are not predictably associated with osteoporosis.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the FRZB gene with osteoporosis or obesity or determine the association of 19524 with obesity or osteoporosis, as the specification does not teach a large sample size, p values less than .05 or confidence levels greater than 95% for a representative number of polymorphisms within FRZB. The specification only teaches a large sample size with statistically significant data for the analysis of an association between high BMI in women and the position 19524 however the specification does not clearly teach the allele associated with high BMI. The specification does not teach statistically significant date ($p<.05$) for the association of the allele at position 19524 and osteoporosis. Furthermore, the specification does not characterize the individuals as having additional disorders that could contribute to obesity or osteoporosis.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the FRZB gene with osteoporosis or obesity in "any" species the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the A allele of G19524A in the FRZB gene to determine if in fact there was either an association between the polymorphism in an human or non-human individuals and obesity or osteoporosis and to determine if 19524 was involved with obesity, BMI index, osteoporosis. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not polymorphisms of FRZB would be responsible for determining the

predisposition to obesity or osteoporosis in any individual as well as unpredictable as to whether the G or A allele of 19524 is indicative increased and decreased risk along with being both protective and predisposing to obesity and osteoporosis. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any osteoporosis and obesity. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

8. The response traverses the rejection on pages 9-10 of the comments mailed 06/01/2009. The response asserts that the claims are drawn to the A allele of G19524 of the human FRZB gene and thus the claims are not drawn to a large variety of polymorphism among a large number of genes in a large number of species, both human and non-human. This response has been thoroughly reviewed but not found persuasive. The claims are not limited to a specific FRZB gene nor are the claims limited to human. The claims encompass analysis of any individual, as demonstrated by the specification individual encompasses any mammal, thus the claims encompass analysis of both human and non-humans. Additionally neither claims nor the specification define FRZB thus FRZB can encompass any frizzle related protein gene, as demonstrated above which encompass number different genes. Thus the claims are broadly drawn to analysis of an A allele at position 19524 in a FRZB in any individual and determining predisposition to risk of developing obesity or osteoporosis. The specification does not provide a

predictable association in a representative number of species to enable one of skill in the art to make and use the invention as broadly claimed.

The response asserts that the specification demonstrates that the association of the A allele of G19524A is associated with obesity, as measure by BMI and the G allele is associated with osteoporosis. This response has been thoroughly reviewed but not found persuasive. The claims are not drawn to determining risk of osteoporosis by detecting the presence of a G allele and determining the G allele is indicative of osteoporosis, the claims recite that the A allele of G19524A is associated with risk of osteoporosis. Therefore even arguendo that the specification would provide support for a predictable association of the G allele of FRZB gene in 19524, the claims do not require nor recite detecting or determining the G allele. Additionally, the specification does not demonstrate a representative number of species, human and non-human individuals as well as homologs and variants of FRZB gene that of the A allele of G19524 that are predictably associated with obesity, therefore the specification does not provide evidence nor demonstrate the predictable association of the A allele of G19524A and its association with risk of obesity or osteoporosis in any individual in any FRZB gene.

The response asserts that Kroese, Hattersly, Ionnidis, and Hegele teach that statistical association of studies are highly inaccurate. The response asserts that Kroese does not contradict the ability of a SNP to be able to predict risk to some degree. The response asserts that these citations are indication of difference of opinion among research community but are not persuasive in demonstrating that the claimed invention is not enabled. The response asserts that Ikegawa is outside the scope of the current claims and thus irrelevant. This response has been thoroughly reviewed but not found persuasive. The references cited demonstrate the knowledge and

understanding of the art and thus demonstrate the highly unpredictably field of SNP association studies. Each of these references provide evidence of the necessary components and what is required to predictably associate one single SNP to risk of disease and the specification does not provide guidance that would enable one of skill in the art to predictably association the A allele of G19524A of any FRZB gene in any human or non-human individual with risk of obesity or osteoporosis. For example Hegele demonstrates the need for replication of initial association of a SNP with a phenotype (see pg. 1059) and the specification does not provide analysis of any replication study, including analysis in male population, any other human population, much less any other species. Thus, the art demonstrates the unpredictably of associating one single SNP with a phenotype, risk of osteoporosis or obesity in the instant case, and the specification does not provide guidance that would allow a skilled artisan to predictably use the claimed invention. Therefore, the references cited demonstrate the unpredictably of the claimed invention. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

9. No claims are allowable.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Sarae Bausch/
Primary Examiner, Art Unit 1634